High-throughput toxicity screening produces human-relevant results

By Thomas Burns Jr.

Using *in vitro* and *in silico* testing in primary human cell systems, scientists reported in the May issue of the journal Nature Biotechnology bioactivity profiles for 776 unique and diverse chemicals with potential for human exposure. The use of a human-relevant system may provide a rapid and accurate screening method to prioritize chemicals for further toxicity testing or to identify new pharmaceutical activities.

"This is the first data manuscript in the field of high throughput toxicity screening [HTS] on such a large number of chemicals to be published in one of the Nature journals," said Nicole Kleinstreuer, Ph.D., the paper's lead author, who is now a contractor supporting the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). "It demonstrates the utility of HTS assays that use human primary cells to elucidate mechanisms of action and predict toxicities for a diverse set of chemicals."

Kleinstreuer's work with NICEATM seeks increase the efficiency of toxicity testing by allowing resources for follow-up testing to be focused on the bioactivities of highest concern. (Photo courtesy of Steve McCaw)

Limitations of traditional toxicity testing

Toxicity data on many chemicals do not exist. The study's authors point out that it is difficult or impossible to test these chemicals for toxicity using traditional animal testing methods, because of the expense, time required, ethical concerns about animal testing, and problems with species extrapolation.

The researchers wanted to examine whether *in vitro* and *in silico* high throughput test methods, especially those using human cell and gene targets, could provide a viable alternative to such testing.

In vitro testing can provide human-relevant results

Scientists from the U.S. Environmental Protection Agency (EPA) tested 776 unique environmental and industrial chemicals, including pesticides, food additives, and pharmaceuticals. The researchers chose eight human primary cell systems, based on their sensitivity to specific drug mechanisms and adverse effects, and recorded 87 different measurements, resulting in 306,240 individual data points.

Pharmaceuticals and pesticides were the most active chemicals, while fragrances and colorants, used in cosmetics and as food additives, proved to be the least active. Only eight percent of the chemicals were uniformly inactive, including a few known to be pharmaceutically active in humans - a finding that highlights both areas for further research as well as the potential need for additional endpoints of study.

Identifying chemicals with previously unknown mechanisms of action

The study's authors reported intriguing results of the cluster analysis. Researchers grouped chemicals that showed a similar endpoint profile, so that specific mechanisms of action could be inferred for each group. For example, analgesics, such as aspirin and the non-steroidal anti-inflammatory drugs Indomethacin and Celecoxib showed similar endpoint profiles, a finding that helped validate this approach.

A seemingly unrelated chemical, propyl gallate, a common cosmetic and food additive, also clustered with this group, suggesting that propyl gallate might have a similar mechanism of action as do the known analgesics. This finding illustrates the potential of this approach to shed light on as yet unrecognized toxicities or mechanisms of action for chemicals, based on profile similarities.

This work was conducted as part of the EPA ToxCast *(http://www.epa.gov/ncct/toxcast/)* Program, which is a member of Tox21, *(http://ntp.niehs.nih.gov/?objectid=06002ADB-F1F6-975E-73B25B4E3F2A41CB)* a federal consortium that includes NIEHS, NTP, EPA, the National Center for Advancing Translational Sciences, and the U.S. Food and Drug Administration. The goal of Tox21 is to develop predictive toxicity models and prioritization schemes based on data from alternative testing methods.

Citation: Kleinstreuer NC, Yang J, Berg EL, Knudsen TB, Richard AM, Martin MT, Reif DM, Judson RS, Polokoff M, Dix DJ, Kavlock RJ, Houck KA.
(http://www.ncbi.nlm.nih.gov/pubmed/24837663)
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